II. REMARKS

Introductory Comments

Claims 21-25 were examined in the Office Action under reply and stand variously rejected under (1) 35 U.S.C. § 112, second paragraph; (2) 35 U.S.C. §112, first paragraph; (3) 35 U.S.C. §102; and (4) 35 U.S.C. §103(a). These grounds of rejection are believed to be overcome by this response and are otherwise traversed for reasons discussed in detail below.

Overview of the Above Amendments

Claims 21, 22 and 25 have been amended to recite the invention with greater particularity. Specifically, the abbreviation "rAAV" has now been spelled-out. Support for the amendment can be found in the original claims and throughout the specification.

The Rejection Under 35 U.S.C. §112, Second Paragraph:

Claims 21-25 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite due to the abbreviation "rAAV." Applicants have amended claims 21, 22 and 25 to spell out the term "rAAV" at each occurrence. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

The Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 21-25 were rejected under 35 U.S.C. § 112, first paragraph. The Office contends "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." Office Action, page 3. The Examiner acknowledges that the specification discloses delivering rAAV expressing AADC to a monkey brain by intrastriatal administration using CED, expression of the AADC in the striatum and conversion of L-dopa to dopamine in the striatum of the monkey brain. Nevertheless, the Examiner argues:

> The claims encompass using a pharmaceutical composition comprising a rAAV expressing any therapeutic protein to the brain of a subject to

provide therapeutic effect for various CNS disorders, such as migraine, Parkinson's disease, Alzheimer's disease, glioma, neuroblastoma, multiple sclerosis, schizophrenia etc., in a subject via various administration routes in addition to CED.

* * *

The specification fails to provide correlation between a therapeutic protein and a particular CNS disorder such that expression of said therapeutic protein could provide therapeutic effect for said particular CNS disorder *in vivo*. Absent such correlation, one skilled in the art at the time of the invention would not know which gene expressing a therapeutic protein should be used for what CNS disorder.

Applicants traverse the rejection and its supporting remarks.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art, without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). In fact, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *Ex parte Forman*, *supra*; *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). For the reasons detailed below, the Office has failed to establish a *prima facie* case of nonenablement.

The Office alleges that the specification fails to provide correlation between a therapeutic protein and a particular CNS disorder. However, at the time of the invention, many CNS disorders and substances necessary to alleviate the disorders, were known. It is axiomatic that a patent specification "need not teach, and preferably omits, what is well known in the art." See, *Spectra-Physics, Inc. v. Coherent, Inc.* 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed.

Cir. 1986). For example, it was known that HSV-tk could be used to treat cancer and viral disorders of the brain. See, e.g., paragraph 4 of the accompanying Declaration Pursuant to 37 CFR 1.131 ("the Declaration"). It was also known, for example, that the enzyme kynurenic acid was deficient in patients with Huntington's disease. See, e.g., Jauch et al., *J. Neurol. Sci.* (1995) 130:39-47. Moreover, it was known that the enzyme AADC was deficient in patients with Parkinson's disease. These are but a few of the many examples of proteins known to be deficient, missing or useful for treating a variety of CNS disorders. One skilled in the art could readily determine, in view of the state of the art and the teachings of applicants' specification (e.g., page 17, lines 7-14; page 10, lines 22-26; page 20, lines 1-10), how to select and use suitable nucleotide sequences. Although certainly not required to establish enablement, multiple working examples regarding selection of sequences, promoters, dosages and routes of administration to treat CNS disorders are also provided in the specification.

Moreover, the present specification clearly sets forth procedures for determining dosage levels, routes of administration of virions and selection and administration of DNA sequences. Applicants direct the Examiner's attention to page 28, line 23 through page 29, line 16 where the specification teaches how to determine dosages of virions and other compounds suitable for treating CNS disorders. The specification describes how to assess the therapeutic effects of the compounds, for example by histological, biochemical, imaging and/or behavioral analysis. Further, representative routes of administration are described in detail, for example throughout the Examples where applicants describe how to perform CED and how to compare this preferred route of administration to other modes of intracranial delivery.

The Office Action cites several references in support of the allegation that gene therapy was unpredictable at the time of filing. In particular, Deonarain, M.P., *Exp. Opin. Ther. Pat.* (1998) 8:53-69 ("Deonarain") is cited for evidencing that "one of the biggest problems hampering successful gene therapy is the 'ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time.'" Office Action, page 5. However, Deonarain has nothing whatsoever to do with AAV-mediated gene therapy. In fact, AAV is not even mentioned in the article. Rather, Deonarain's review is directed to ligand-targeted receptor-mediated vectors, a

wholly different delivery mechanism than applicants'. Further, a search on the literature database Medline did not turn up any articles authored by Deonarain that had to do with AAV-mediated gene delivery. Accordingly, Deonarain cannot be considered one of skill in the art relevant to the present invention.

Moreover, Eck et al., Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, p. 77-101 (1996) and Gorecki, *Exper. Opin. Emerging Drugs* (2001) 6:187-198 are general review articles that devote only a few paragraphs at best to AAV-mediated gene therapy. Indeed, solving the problems discussed in these references is precisely the issue addressed by applicants. The references cited by the Office evidence that prior to applicants' invention, there was a need for improved methods of delivering genes to the CNS. However, establishing that there were problems with known delivery systems does not in any way establish that applicants' specification is not enabling. In fact, applicants' specification describes and demonstrates effective delivery of rAAV virions carrying a representative gene for the treatment of a representative CNS disorder to appropriate regions of the brain and that this gene provides a therapeutic effect, namely restoration of dopaminergic activity in Parkinson's patients (*i.e.* MPTP-lesioned monkeys). In light of applicants' teachings, the references cited by the Examiner do not provide evidence of unpredictability.

Additionally, subsequent to applicants' filing, there has been a myriad of publications demonstrating the almost universal applicability of the use of AAV-mediated gene delivery to treat CNS disorders. A number of abstracts detailing the utility of the AAV vector system for use in the context of CNS disorders are attached.

Finally, the inventors herein have attested in the accompanying Declaration that one of skill in the art of AAV-mediated gene therapy could indeed follow the teachings in the application to prepare recombinant AAV virions including genes encoding proteins for the treatment of CNS disorders, and deliver the virions to subjects with widespread distribution of virions to provide a therapeutic effect. As enablement is judged from the perspective of the skilled artisan, the Office's rejection of the claims under 35 U.S.C. §112, first paragraph cannot stand.

Contrary to the Office's assertions, then, applicants have indeed adequately enabled the claimed invention in the specification such that one of skill in the art could

make and use the invention without an undue amount of experimentation. Based on the foregoing, applicants submit that more than adequate evidence of enablement has been provided. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Rejections Under 35 U.S.C. §102:

Claim 21 was rejected under 35 U.S.C. §102(a) as anticipated by Mizuno et al., *Jpn. J. Cancer Res.* (January 1998) 89:76-80 ("Mizuno"). Claims 21 and 25 were also rejected under 35 U.S.C. §102(a) as anticipated by Leff et al., Leff et al., "*Towards a gene therapy for Parkinson's disease (PD): Intrastriatal injection of recombinant adeno-associated virus (rAAV) encoding human L-aromatic amino acid decarboxylase (hAADC) in 6-OHDA lesioned rats restores AADC activity to control levels*" from the 27th Annual Meeting of the Society for Neuroscience, Part 1, New Orleans, LA, October 25-30, 1997 ("Leff"). Applicants are submitting herewith a Declaration Pursuant to 37 CFR 1.131 ("the Declaration") evidencing that they were in possession of the invention prior to October 1997, hence, prior to both Mizuno and Leff. Thus, these bases for rejection have been overcome and withdrawal thereof is respectfully requested.

Claim 21 was also rejected under 35 U.S.C. §102(b) as anticipated by Okada et al., *Gene Ther.* (1996) 3:957-964 ("Okada"). The Office states that Okada teaches the stereotactic delivery of AAV-tk-IRES-IL-2 particles into the tumor in the brain of nude mice with a reduction in the mean volume of the tumors as compared to controls. Office Action, page 8. However, Okada does not show the widespread distribution of rAAV virions as required by applicants' claims. Rather, Okada only demonstrates expression along the needle track. See, the abstract and page 960, column 1. Thus, Okada does not anticipate the present claims and withdrawal of this basis for rejection is respectfully requested.

The Rejection Under 35 U.S.C. §103(a):

Claims 21-25 were rejected under 35 U.S.C. §103(a) as obvious over Okada in view of PCT Publication No. WO 95/34670 to Johnson ("Johnson") and Zhu et al., *Gene Ther.* (1996) 3:472-476 ("Zhu"). However, applicants submit the Office has failed to

provide a *prima facie* case of obviousness.

In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. *In re Vaeck* , 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the Office has failed to satisfy these criteria and therefore has not presented a *prima facie* case of obviousness.

In particular, claim 21 recites a method of delivering recombinant AAV virions to the brain of a subject suffering from a CNS disorder by administering a composition to the brain of the subject such that widespread distribution of the recombinant AAV virions is achieved. None of the cited references, taken alone or together, teach or suggest such a method. As explained above, the primary reference, Okada, does not disclose the widespread delivery of recombinant AAV virions to the brain. Johnson and Zhu do not cure the defects of Okada. Johnson's mice, as with Okada's, are delivered recombinant AAV using stereotactic injection (see, Example 9). As shown in Okada, such delivery only provides for local transduction. Moreover, Johnson does not even deliver a therapeutic protein, but rather β-galactosidase. Zhu does not pertain to viral-mediated gene delivery, let alone recombinant AAV virion delivery. Rather, Zhu relates to liposome-mediated gene transfer. Recombinant AAV virions and liposomes are completely different. Notably, liposomes are not proteinaceous and would therefore be expected to interact with a cellular membrane in a dramatically different way than AAV. Accordingly, there is absolutely no suggestion or motivation to modify Okada as asserted, there is no reasonable expectation of success, and the references do not teach or suggest all of the claim limitations.

Therefore, it appears the Office is using the teachings provided by applicants' disclosure to piece together teachings from Okada, Johnson and Zhu and arrive at the subject matter of the claims. This is merely a hindsight reconstruction of applicants' invention, using applicants' own disclosure as prior art. It is well established that the

Office cannot use a claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritch* 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). See, also *In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("one cannot use hindsight reconstruction to pick and chose among isolated disclosures in the prior art to deprecate the claimed invention.")

The Office Action has failed to identify the requisite teaching or motivation from the prior art to arrive at applicants' invention. Without the benefit of applicants' disclosure, there is no motivation or suggestion to one of ordinary skill in the art to combine the cited references to render the methods claimed. Thus, the instant grounds of rejection are improper. Reconsideration and withdrawal of the '103 rejections is respectfully requested.

III. CONCLUSION

In view of the foregoing, applicants submit that the claims are now in condition for allowance and request early notification to that effect. If the Examiner notes any further matters which the Examiner believes may be resolved by a telephone interview, the Examiner is encouraged to contact Christina Thomson by telephone at (510)748-7208, or by fax at (510)748-7368.

Respectfully submitted,

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